



Beyond Anthrax:

Confronting the Future
Biological Weapons Threat



MAY 2004



JIM TURNER, RANKING MEMBER
SELECT COMMITTEE ON HOMELAND SECURITY

Beyond Anthrax: Confronting the Future Biological Weapons Threat

Jim Turner, Ranking Member
House Select Committee on Homeland Security

228 Adams Building
101 Independence Avenue, SE
Washington, DC 20540
202-226-2616
<http://www.house.gov/hsc/democrats/>

Table of Contents

~

Executive Summary.....	i
Today's Biological Weapons: Using Nature to Cause Harm	1
Tomorrow's Biological Weapons: Using Biotechnology to Change Nature	2
<i>The Soviet Biological Weapons Program</i>	2
<i>The Power of Modern Biotechnology</i>	3
The 'Dual-Use' Dilemma	4
Defending Against Biological Weapons	5
<i>Prevention</i>	6
<i>Preparedness</i>	6
<i>Protection</i>	6
Project Bioshield: A Static Defense Against a Changing Threat	7
<i>The Response to SARS</i>	7
<i>The Perennial Threat of Flu</i>	8
Building a Biodefense Strategy for Future Threats	8
<i>Broad-Spectrum Protections Against Pathogens</i>	8
<i>Recommendation</i>	10
<i>Rapid Countermeasures Development and Production: Moving Fast from</i> <i>Bug-to-Drug</i>	10
<i>Recommendation</i>	14
Conclusion	15

Executive Summary

The threat to national security posed by “classical” biological weapons is severe, but it pales in comparison to the potential scourges of the future. Today’s bioterrorist threat is rooted in the natural world of pathogens that have existed in the environment for millennia. For years, the fundamental properties that made them useful as weapons could not be altered by military scientists. Instead, these basic properties were harnessed in combination with technologies such as stabilizing agents and delivery mechanisms to make usable weapons.

As we progress into the future, the nature of the biological weapons threat will change. The rapidly expanding power and capabilities of biotechnology are allowing a greater number of technically-trained workers around the globe to more easily alter the fundamental properties of existing and potential pathogens. The biological weapons programs of the Soviet Union and multiple reports in scientific journals have already demonstrated approaches to changing key traits such as contagiousness and virulence, as well as the capability to engineer resistance to vaccines and drugs, evasion of detection mechanisms, and the creation of totally new pathogens with unique properties. While virtually all such research is currently conducted for peaceful purposes, the possibility exists that motivated researchers could apply these techniques to bioengineer new weapons exists.

Confronting the danger posed by these advanced biological weapons is a challenge we must begin today. Biotechnology is fundamentally “dual-use.” It can be used both for peaceful and destructive purposes. Because of its potential for misuse, balanced biodefense policies must be developed and adopted to ensure our safety and security. These should include reasonable steps to prevent the spread of dangerous pathogens and the technology to alter their properties. Preparedness of our health infrastructure must also be enhanced and maintained. Finally, protective treatments, including drugs and vaccines, to counter potential weaponized pathogens need to be available when a crisis occurs.

It is in the area of protections for tomorrow’s biological weapons threat that we are particularly weak. The primary proposal advanced to boost our protection capacities, Project Bioshield, will not address this threat. Bioshield is targeted at addressing classical agents, not the laboratory-altered pathogens of the future. In addition, it relies on the current process of drug and vaccine development, which takes an average of 14 years before a new medicine is available. As a consequence, our protective biodefenses are essentially static and unmoving in the face of a threat that is highly variable and unpredictable. As illustrated by SARS, we lack effective countermeasures and a nimble way to develop and field them.

New capabilities are required to specifically address the threat of emerging or bioengineered pathogens. These must include new medicines that target a broad range of pathogens or stimulate the immune system. It will also require a concerted effort to reduce the long timeframe of drug development, so that we can move from “bug-to-drug” in months or weeks, rather than years. Both of these additions to our biodefenses face significant hurdles, but they are necessary elements. They are also unlikely to be forthcoming without targeted federal policies and commitment.

Biodefense research and procurement policies for medical countermeasures must be designed to yield broad-spectrum approaches. In addition, a concerted, organized effort must be developed and launched to build a rapid response capability for developing new medicines should a novel or bioengineered pathogen emerge or be deployed against us. The current drug and vaccine development process has suffered from a lack of research-attention to key bottlenecks, such as early and accurate prediction of safety and efficacy. Financial, organizational, regulatory, and other barriers have blocked sufficient investment in these problems thus far. New, targeted research and development, as well as government access to capabilities and the technologies necessary for rapid development and delivery of cures will be necessary. A major effort in this area of biodefense is warranted not only because of the serious danger of biological weapons today and in the future, but because enormous benefits to public health and economic well-being will inevitably be derived from such an investment.

Beyond Anthrax: Confronting the Biological Threat of the Future

The threat to national security posed by “classical” biological agents such as smallpox and anthrax is severe and the federal government’s response is thus far incomplete. But this current threat pales in comparison to the potential scourges of the future. Biotechnologies that have and are being developed for peaceful, beneficial purposes can also be used to bioengineer pathogens, with the potential to create more virulent, more contagious, and wholly resistant strains of bacteria and viruses. Many of our current medicines and vaccines can be defeated through bioengineering, and the existing system of drug and vaccine development is too slow and cumbersome to address this emerging threat. Providing security for the decades to come requires that we start preparing for this threat now.

Our biodefense efforts must be geared towards developing broad-spectrum protections against infectious diseases and radically shortening the time it takes to move from “bug” to “drug.” Unless we start these initiatives now, terrorists and enemy states developing the weapons of the future will be far ahead of our defense efforts. The free world cannot allow this to happen.

Today’s Biological Weapons: Using Nature to Cause Harm

Today’s bioterrorist threat is rooted in the natural world of microbes. The biological weapons we are now most concerned about, such as anthrax, smallpox, and tularemia, have existed in the environment for millennia.¹ Man has collected these pathogens and applied them to use as biological weapons. Modern bioweapons programs conducted by governments emerged during and soon after World War II, and continued through the rest of the century.² Military scientists identified specific biological pathogens in nature that could cause harm to people, animals or plants, examined their natural properties, and harnessed these properties in combination with technologies such as stabilizing agents and delivery mechanisms like artillery shells to weaponize them. The product was effective weapons for use on the battlefield or against an enemy civilian population or infrastructure. Often referred to as the “classical agents,” the essential properties of these microbes, such as stability, toxicity, and contagiousness, could not be altered. Anthrax has characteristics that allow for persistence in the environment and easy spread through the air, but it is not contagious, and could not be made so through weaponization. Smallpox virus, while a highly dangerous and infectious disease, is susceptible to a vaccine. As a result, near universal vaccination made smallpox useless as a weapon during much of the 20th century.

Despite the inherent limitations of classical agents, the threat from today’s biological weapons is substantial and growing. Anthrax remains extremely dangerous and highly lethal when used as an agent of war or terror. In other cases, our health practices have changed. For example, with smallpox, most Americans under the age of 30 have never been vaccinated, leaving the population vulnerable to attack.³ Because people travel more frequently and over longer dis-

¹ Centers for Disease Control and Prevention, *Emergency Preparedness and Response: Bioterrorism Agents/Diseases*, November 2003, <http://www.bt.cdc.gov/agent/agentlist-category.asp>.

² William Broad, Judith Miller, Stephen Engelberg, *Biological Weapons and America’s Secret War*, (New York: Simon and Schuster, 2001).

³ Democratic Members of the House Select Committee on Homeland Security, *A Biodefense Failure: The National Smallpox Vaccination Program One Year Later*, January 2004, http://www.house.gov/hsc/democrats/pdf/press/040129_ABIodefenseFailureOneYearLater.pdf.

tances, contagious diseases can spread farther, faster. Improvements in science and technology have also contributed particularly to the threat of bioterrorism. The skills and equipment required to collect and grow pathogens have become more widespread, less expensive, and more user-friendly.⁴ As the anthrax attacks demonstrated, biological weapons production and use do not require large government programs and costly weapons systems to be effective killers. But while the threat of today's biological weapons remains very serious, it is essential to recognize that the danger posed by these "classical agents" is rooted in the past, not the future.

Tomorrow's Biological Weapons: Using Biotechnology to Change Nature

The explosion in the power and potential of biotechnology is making the future biological weapons threat a reality. According to a panel of expert scientists assembled by the Central Intelligence Agency, "advances in biotechnology, coupled with the difficulty in detecting nefarious biological activity, have the potential to create a much more dangerous biological warfare threat."⁵ Using new techniques and knowledge, weapon makers are no longer limited to the properties inherent to the pathogens in nature. They can manipulate the basic biology of the pathogens themselves in order to alter and enhance key properties useful for bioweapons, such as transmissibility, stability, virulence, or the range and types of animals, and humans, a pathogen can infect.⁶ Others changes can be made that render normally effective detectors, drugs, vaccines and even natural bodily defenses impotent against a modified pathogen. Ultimately, as the understanding of human and microbial biology expands, wholly new agents with devastating effects on people, animals, or plants can be created.

The Soviet Biological Weapons Program

Science and technology applicable to the production of the next generation of biological weapons emerged some time ago. Although the United States ceased its offensive biological weapons programs in 1969,⁷ the Soviet Union continued to conduct a secret program throughout the Cold War.⁸ Soviet scientists and engineers used biotechnologies developed during the 1970's and 80's in a large-scale, well funded program to develop and weaponize both classical agents and new, engineered weapons. In addition to the production of tons of anthrax, smallpox, tularemia, and other agents for use in missiles, shells, and bombs, Soviet scientists reportedly worked to genetically modify classical agents to develop new properties, such as higher pathogenicity, the display of unusual symptoms, and antibiotic or vaccine resistance. Experimentation also involved testing combinations of pathogen genomes to explore exotic killing properties, including the design of "binary agents," pairs of pathogens that do not coexist in nature, combined to cause severe

⁴ National Research Council, *Biotechnology in the Age of Bioterrorism*, (Washington, D.C.: National Academy Press, 2004):13-14, 17-18.

⁵ Office of Transnational Issues, Central Intelligence Agency, *The Darker Bioweapons Future*, OTI SF 2003-108, November 3, 2001, <http://www.fas.org/irp/cia/product/bw1103.pdf>.

⁶ James Petro, Theodore Plasse, Jack McNulty, "Biotechnology: Impact on Biological Warfare and Biodefense," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, 1, no. 3, (2003):161-168.

⁷ U.S. Department of the Army, *U.S. Army Activity in the U.S. Biological Warfare Programs* (Unclassified), Volume 1, February 24, 1977, http://www.gwu.edu/%7Eensarchiv/NSAEBB/NSAEBB58/RNCBW_USABWP.pdf.

⁸ Ken Alibek, *Biohazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World*, (New York: Random House Inc., 1999).

and difficult to treat disease.⁹ While many programs were experimental, antibiotic resistant plague and anthrax, as well as a strain of plague genetically engineered to express diphtheria toxin, may have been weaponized by the Soviet military.¹⁰

The Power of Modern Biotechnology

While many of the details and specific activities of the Soviet biological weapons program are still unknown, none of the reported experiments or weapons were beyond scientific capabilities at the time.¹¹ Today, techniques for genetic and microbial manipulation, as well as for production of microbes and other biological material, are more advanced and are rapidly improving.¹² In academic, private, and government laboratories, scientists and engineers are spending enormous time, effort, and money to expand these capabilities as quickly as possible, most commonly in pursuit of medical advances. As part of this enterprise, scientists engineer pathogens and alter their natural properties.¹³ For example, the introduction of genes into microbes in order to render them immune to antibiotics is a standard practice in biology. The development of viruses that can evade the human immune system's defenses is an important goal of gene therapy research.¹⁴

Specific experiments involving the manipulation of dangerous pathogens with modern techniques have already been reported. Scientists have made the tuberculosis bacterium more virulent¹⁵ and are purposely trying to modify the Asian flu virus to find out if it could evolve to transmit between humans.¹⁶ Researchers have demonstrated their ability to genetically engineer viruses, including close analogs of smallpox, to kill animals vaccinated against the natural pathogen.¹⁷ Engineered resistance to existing anthrax vaccines has also been demonstrated¹⁸ and attempts to repeat this work are reportedly underway at the Department of Defense.¹⁹ Scientists have also used non-living, commercially available chemicals to recreate the polio virus, the cause

⁹ Mark Williams, "The Looming Threat," *Acumen*, 1, no. 4 (November/December 2003): 41-50.

¹⁰ "Interview with Sergei Popov," *Journal of Homeland Security*, November 2000, http://www.homelandsecurity.org/journal/Interviews/PopovInterview_001107.htm.

¹¹ David Huxoll, "Biological Weapons Proliferation and the New Genetics," Testimony before the Senate Committee on Government Affairs, May 17, 1989.

¹² Claire Fraser and Malcolm Dando, "Genomics and Future Biological Weapons: The Need for Preventative Action by the Biomedical Community," *Nature Genetics*, 29, no. 3 (2001):253-256.

¹³ Kathryn Nixdorff and Wolfgang Bender, "Biotechnology: Ethics of Research and Potential Military Spin-off," *International Network of Scientists and Engineers Against Proliferation News Bulletin*, 19 (March 2002):19-22; http://www.inesap.org/pdf/INESAP_Bulletin19.pdf.

¹⁴ We-Shau Hu and Vinay Pathak, "Design of Retroviral Vectors and Helper Cells for Gene Therapy," *Pharmacological Reviews*, 52, no. 4 (2000):493-511.

¹⁵ (a) Nobuyuki Shiono and others, "Hypervirulent Mutant of *Mycobacterium tuberculosis* Resulting from Disruption of the *mce1* Operon," *Proceedings of the National Academy of Sciences*, 100, no. 26 (2003):15918-15923; (b) Oliver Wright, "Scientists' Bid to Combat TB Made It More Virulent," *London Times*, December 27, 2003.

¹⁶ Rachel Nowak, "Superflu Is Being Brewed in the Lab," *NewScientist.com*, February 26, 2004, <http://www.newscientist.com/news/news.jsp?id=ns99994713>.

¹⁷ (a) Ronald Jackson and others, "Expression of Mouse Interleukin-4 by a Recombinant Estromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology*, 75, no. 3 (2001): 1205-10; (b) William Broad, "Bioterror Researchers Build a More Lethal Mousepox," *New York Times*, November 1, 2003.

¹⁸ A.P. Pomerantsev and others, "Expression of Cereolysin AB Genes in *Bacillus anthracis* Vaccine Strain Ensures Protection Against Experimental Infections," *Vaccine*, 15, no. 17-18 (December 1997):1846-1850.

¹⁹ Judith Miller, Stephen Engelberg, William Broad, "U.S. Germ Warfare Research Pushes Treaty Limits," *New York Times*, September 4, 2001, A1.

of a debilitating, communicable disease and the current target of a worldwide effort to eradicate the naturally occurring pathogen.²⁰ Similar experiments have been conducted with the Ebola virus.²¹ The entire genetic blueprints of plague, anthrax, and Marburg virus, among other microbes, have been determined and made openly available,²² and efforts to understand and manipulate the functions of their genes are ongoing.²³

The alteration of the genetic structure of viruses and bacteria is common practice in laboratories around the world. Available techniques allow the identification and manipulation of specific cellular components related to a pathogen's virulence, host range, and other traits, as well as the incorporation of novel, tailor-made traits such as antibiotic resistance.²⁴ Other technologies allow very specific targeting, potentially for disruption, of biological process vital for health.²⁵ Virtually all such research is being conducted for peaceful purposes. However, according to the Defense Science Board, the science and technology advisors for the military, "motivated researchers using advanced genetics techniques can engineer pathogens with unnatural characteristics that enhance their offensive properties by altering such characteristics as stability, dissemination properties, host range, contagiousness, resistance to drugs and vaccines, and persistence in the environment, among others."²⁶

The 'Dual-Use' Dilemma

Biotechnology will predictably become more advanced and more widespread over the next several decades. This progress is driven forward by the numerous desirable products and commercial opportunities that biotechnology, already a vibrant economic sector, will provide, such as new medicines, agricultural products, and materials. Meanwhile, the know-how and capability to utilize this technology is spreading rapidly and globally. As the technology evolves, more mature methods and techniques become progressively less expensive and easier to use, reducing the costs

²⁰ (a) Jeronimo Cello, Aniko Paul, and Eckhard Wimmer, "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template," *Science*, 297, no. 5583 (August 9, 2002): 1016-18; (b) Rick Weiss, "Polio-Causing Virus Created in N.Y. Lab: Made-From-Scratch Pathogen Prompts Concerns About Bioethics, Terrorism," *Washington Post*, July 12, 2002.

²¹ Shinji Watanabe and others, "Production of Novel Ebola Virus-Like Particles from cDNAs: an Alternative to Ebola Virus Generation by Reverse Genetics," *Journal of Virology*, 78, no. 2 (2004): 999-1005.

²² (a) J. Parkhill and others, "Genome Sequence of *Yersinia pestis*, the Causative Agent of Plague," *Nature*, 413, no. 6855 (October 4, 2001): 523-27; (b) T.D. Read and others, "The Genome Sequence of *Bacillus anthracis* Ames and Comparison to Closely Related Bacteria," *Nature*, 423, no. 6935 (May 1, 2003): 23-5; (c) A. Bukreyev and others, "The Complete Nucleotide Sequence of the Popp (1967) Strain of Marburg Virus: a Comparison with the Musoke (1980) Strain," *Archives of Virology*, 140, no. 9 (1995): 1589-1600.

²³ For example, see Viktor Volchkov and others, "Recovery of Infectious Ebola Virus from Complementary DNA: RNA Editing of the GP Gene and Viral Cytotoxicity," *Science*, 291, no. 5510 (March 9, 2001): 1965-1969.

²⁴ For example, see Gary Kobinger and others, "*Filovirus*-pseudotyped Lentiviral Vector Can Efficiently and Stably Transduce Airway Epithelia *In Vivo*," *Nature Biotechnology*, 19, no. 3 (March 2001): 225-230 and other references in this section.

²⁵ (a) Mark Wheelis, "Biotechnology and Biochemical Weapons," *The Nonproliferation Review*, (Spring 2002): 48-53; (b) for a specific example, see Yari Dorsett and Thomas Tuschl, "siRNAs: Applications in Functional Genomics And Potential as Therapeutics," *Nature Reviews Drug Discovery* 3, no. 4 (April 2004): 318-329.

²⁶ Defense Science Board, 2001.

and expertise required to manipulate pathogens genetically.²⁷ Further simplifying the process, the vast majority of biological scientific and technological information is public, and access is increasingly available on-line. In balance, these outcomes are expected to be major contributors to economic growth and human well-being. But biotechnology will also bring a significant element of danger and potential for misuse at the hands of criminals, terrorists, or foreign enemies. In this sense, it has a “dual-use,” for both good and evil. According to John Gannon, former deputy director for intelligence at the CIA, “the continuing revolution in science and technology will accentuate the dual use problem related to biotech breakthroughs...Responsible scientists will have an extraordinary opportunity to improve the quality of human life across the planet. At the same time, terrorists and other evildoers may develop a powerful capability to destroy that life.”²⁸

A parallel can be drawn between biotechnology and nuclear technology, which emerged with the splitting of the atom in the mid-twentieth century. While nuclear weapons contributed to victory over Japan and peace during the Cold War, the nightmare of a potential nuclear war has been with us for decades and the nuclear terrorist threat has grown recently. Nuclear technology also brings the potential for unlimited energy, but raises still unresolved issues of nuclear waste and safety. As nuclear technology developed and we sought to derive its benefits, our nation adopted and continues to refine responsible and appropriate policies to try to ensure our safety and security. Now, the power and potential of biotechnology is becoming clear. It is again time to understand this new technology and develop balanced policies in biodefense to ensure our safety and security.

Defending Against Biological Weapons

Following the terrorist attacks of September 11, 2001 and the anthrax mailings, Congress and the Administration worked vigorously to strengthen our defenses against the use of biological weapons. The three pillars of biodefense include prevention, such as improvements in the domestic and international security of dangerous pathogen stocks, preparedness, such as the stockpiling of medical supplies, the strengthening of the public health and healthcare delivery infrastructure, and the development and deployment of detection technologies, and protection, the development of drugs and vaccines to treat those who might become infected. As described in a recent report by the Democratic Members of the Select Committee on Homeland Security, some of these policies require revision.²⁹ But they are all important elements in a defense against today’s biological weapons threat. Unfortunately, the application of modern biotechnology to biological weapons development will soon render some of these efforts obsolete, unless we alter our biodefense strategy. While the Administration has recently noted this threat in a statement of biodefense policy, no specific strategy has been made available.³⁰

²⁷ Robert Carlson, “The Pace and Proliferation of Biological Technologies,” *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, 1, no. 3 (2003):1-12.

²⁸ John Gannon, “Viewing Mass Destruction Through a Microscope,” *New York Times*, October 11, 2001, E10.

²⁹ Democratic Members of the House Select Committee on Homeland Security, “Preventing Attacks Through Biodefense and Preparedness,” *America at Risk: Closing the Security Gap*, February 2004, pp. 20-34, www.house.gov/hsc/democrats/pdf/press/report/PreventingAttacksthroughBiodefensePreparedness.pdf.

³⁰ The White House, *Biodefense for the 21st Century*, April 2004, www.whitehouse.gov/homeland/20040430.html.

Prevention

Preventing the use of biological weapons will always be the ideal way to confront this threat, but it is also the most difficult. While it is unlikely that other nations will use biological weapons against the United States or our allies because of the potential for massive retaliation, rogue states or terrorist groups may find such weapons useful. Biological weapons are capable of causing mass casualties and a great deal of fear, and can be difficult to trace for attribution. For those seeking these weapons, prevention consists of restricting access to dangerous pathogens and the technology and information required to exploit them. Unfortunately, these strategies are limited. Microbes are ubiquitous, and many dangerous pathogens, such as anthrax and Ebola, can be collected from the environment. Theft and transport of microscopic quantities of microbes, which can later become the “seed” for cultivating much larger quantities, is relatively easy. In addition, production of weapons is easily concealed.³¹

Ultimately, the “dual-use” dilemma described above makes many restrictions problematic. Access to microbes, research tools, and the information to use them are necessary to realize the benefits of biotechnology, including a robust biodefense. Moreover, as the power and potential of biotechnology is realized, restrictions could be circumvented. Harmless microbes could be made dangerous or artificial ones created from unrestricted materials. Some steps can be taken to limit the spread of dangerous biotechnologies, such as the recent establishment of a *National Science Advisory Board for Biosecurity*³² to monitor research and the adoption of strong international biosecurity regimes.³³ However, as long as enemies with interest in biological weapons exist, the utility of prevention in biodefense is likely to be limited.

Preparedness

Preparedness is essential for defense against both today’s and tomorrow’s biological weapons threat, as well as natural infectious diseases. The early detection of a pathogen release or of illness in the population is critical to enable rapid delivery of care. A strong and properly prepared public health and healthcare delivery infrastructure is then needed to provide treatment and protection to the public. But a primary requirement of preparedness is the availability of medicines and treatment options with which to stop spreading infections, save lives, and reduce suffering. Without this protection, our biodefenses will fail.

Protection

It is in the essential area of protection that the nations’ defense against the biological weapons is the weakest for both today’s and tomorrow’s threat. According to the Defense Science Board, we are seriously unprepared for the 18 most dangerous biological agents, with only one “countermeasure” that can be widely distributed to the public with minimal risk of side-effects.³⁴ Gaps in vaccine and drug protection strategies exist across the spectrum of potential pathogens.

³¹ Jonathan Tucker, *Biosecurity: Limiting Terrorist Access to Deadly Pathogens*, Peacworks no. 52, (Washington, D.C.: United States Institute of Peace, November 2003): 15-18.

³² *National Science Advisory Board for Biosecurity*, <http://www.biosecurityboard.gov/index.htm>.

³³ National Research Council, *Biotechnology in the Age of Bioterrorism*, (Washington, D.C.: National Academy Press, 2004).

³⁴ Defense Science Board, Department of Defense, “The Projected Evolution of Diagnostics, Vaccines, and Therapeutics Against Major Biogents with Strategic R&D and Supply Actions,” *2000 Defense Science Board Summer Study*, (2000).

A proposal to address these gaps, Project Bioshield, has been advanced by the Administration and approved by the House of Representatives. Although a wise first step in shoring up our biodefenses against today's biological weapons, Project Bioshield will not address the biological weapons threat of the future.

Project Bioshield: A Static Defense Against a Changing Threat

In its current form, Project Bioshield will establish a procurement process for obtaining bio-defense medical products from the private sector.³⁵ In expectation of Project Bioshield, and utilizing current authorities and appropriations, the Departments of Defense, Homeland Security and Health and Human Services are already acting to research and acquire new vaccines for anthrax, smallpox, Ebola, and botulinum toxin, new treatments for smallpox and plague, and several other products.³⁶ However, all of these pathogens are well known "classical" agents, broadly recognized as potential threats. The current lack of research and therapeutic strategies required to understand and combat these "classical" agents is not a result of their novelty. Instead, they have simply been ignored for decades by most scientists and pharmaceutical and vaccine developers. Today, even as significant numbers of scientists finally pay attention to countering these infectious agents, the new countermeasures they develop run the risk of becoming obsolete soon after they are produced as our enemies learn ways to engineer around them or new, unforeseen pathogens emerge.

When confronted with a new or engineered agent for which no treatment exists, the existing science and technology does not react quickly enough to provide protection. Today, it takes an average of 14 years to negotiate the drug or vaccine development process and introduce a new medicine. This timeframe is getting longer, rather than shorter.³⁷ Costs are also rising according to industry figures, having grown 55 percent over the last five years to reach \$800 million to \$1.7 billion.³⁸ As a consequence of the time and effort required to respond, our biodefenses are essentially static and unmoving in the face of a threat that is highly variable and unpredictable. To understand the danger of this situation, one need look no further than recent responses to naturally occurring pathogen threats.

The Response to SARS

The world's experience with Severe Acute Respiratory Syndrome (SARS) demonstrated that new infectious diseases can emerge and spread far more quickly than our ability to respond. The virus that caused the disease was identified, isolated and genetically sequenced within two months of the detection of the outbreak.³⁹ Nevertheless, one year later, no broadly applicable or

³⁵ Congressional Research Service, *Project Bioshield*, by Frank Gottron, RS21507, February 6, 2004.

³⁶ (a) National Institutes of Allergies and Infectious Diseases, National Institutes of Health, *NIAID Biodefense Research Agenda for CDC Category A Agents*, publication no. 03-5308, February 2002; (b) National Institutes of Allergies and Infectious Diseases, National Institutes of Health, *NIAID Biodefense Research Agenda for CDC Category B and C Priority Pathogens*, publication no. 03-5315, January 2003.

³⁷ Joseph A. DiMasi, Ronald W. Hansen, and Henry, G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics*, 22, no. 2 (2003):151-185.

³⁸ (a) Peter Landers, "Cost of Developing a New Drug Increases to About \$1.7 Billion" *Wall Street Journal*, December 8, 2003; (b) Jim Gilbert, Preston Henske, and Ashish Singh, "Rebuilding Big Pharma's Business Model," *In Vivo: the Business and Medicine Report*, 21, no. 10, (November 2003):73.

³⁹ Congressional Research Service, *SARS: Public Health Situation and U.S. Response*, by Judith Johnson, RL31937, May 23, 2003.

reliable diagnostic test for the virus has been developed. No existing treatment has been shown to be effective and no new ones have been developed. A vaccine remains years away.⁴⁰ If a pathogen with a much greater lethality or contagiousness than SARS were to emerge as quickly, the cost in lives and economic impact for a defenseless world population would be extremely high.

The Perennial Threat of Flu

Although a well-understood cause of disease, the constantly changing influenza virus continues to challenge us. The best protection available is a flu vaccine, produced every year by industry and purchased by governments for distribution to the public. However, during the flu season of 2003-2004, the United States experienced insufficient supplies of this vaccine.⁴¹ In addition, the vaccine that was available was only moderately effective because its formula, which must be predicted months in advance of the season, was incompatible with the strain of virus that actually emerged. Both of these problems stem from continued reliance on an outmoded manufacturing process, now decades old. The capability to respond quickly to the observed strain of virus and produce quantities that meet actual demand does not exist.

The lack of this capability is particularly worrisome because influenza virus also possesses the capability to mutate dramatically, causing a massive outbreak of widespread, highly contagious, and severe illness. The last time this occurred it caused the influenza pandemic of 1918, which infected one-fifth of the world's population.⁴² Historians estimate that as many as 40 million people were killed, mainly adult men and women between the ages of 20 and 40. Experts believe this global epidemic originated in Kansas. Today, far more extensive and rapid travel and greater population density would probably cause a flu pandemic to spread much more quickly. If such a pandemic were to arise suddenly, we would not have the capability to respond in time with effective therapeutic and vaccination strategies that could save millions of lives.⁴³

Building a Biodefense Strategy for Future Threats

Faced with new or bioengineered pathogen threats for which we have no defense, the only option available today is to predict ahead of time what pathogens we might face, and to begin countermeasure development, production, and stockpiling before any attack or epidemic. But this is not a practical strategy given the time and enormous cost involved, combined with the diversity and unpredictable nature of potential threat agents. The capabilities we need to confront new or bioengineered pathogens fall into two distinct categories, both of which seek to harness the emerging power and potential of biotechnology.

Broad-Spectrum Protections Against Pathogens

Today, some of the most powerful medicines available against microbes are capable of killing a broad range of organisms, rather than just a single type. In the same way that many substances are toxic to both humans and animals, these drugs disrupt common life-sustaining mechanisms that different types of pathogens need to survive. New countermeasures that employ

⁴⁰ Richard Ingham, "SARS Vaccine Lies Several Years Away." *Agence France Presse*, March 4, 2004.

⁴¹ Lawrence Altman, "The Big Bad Flu, or Just the Usual?" *New York Times*, December 14, 2003, A3.

⁴² John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague In History*, (New York: Viking Press, 2004).

⁴³ Anita Manning, "CDC Warns of Pandemic Dangers Posed by Avian Flu," *USA Today*, March 1, 2004.

similar strategies are required. These may include new broad-spectrum drugs against bacteria and viruses likely to be used as weapons which target mechanisms so essential that bioengineers will have a difficult time making pathogens immune.⁴⁴ Other approaches will involve ways to enhance the human body's own defense mechanisms. Our first line of defense, the innate immune response, attacks all invading organisms. An effective capability might involve drugs that boost this system shortly before or after an attack, killing any and all pathogens.⁴⁵ Another might involve therapies targeting common toxic syndromes caused by pathogens, such as sepsis and acute respiratory distress syndromes (ARDS). Our adaptive immune system, which can be made to recognize specific pathogen elements, could be stimulated by the use of vaccines to detect and neutralize broad ranges of pathogens sharing key characteristics.⁴⁶ These are only a few ways broad-spectrum protections against biological weapons might be useful.

While promising, broad-spectrum approaches to protection face many hurdles. For example, moving the human immune system into "high-gear" could trigger over reactions that could damage health or lead to chronic illnesses. Viruses such as HIV, which causes AIDS, have developed to specifically target and undermine the immune system. Bacteria and viruses have also proven capable of developing resistance to existing broad-spectrum antimicrobial drugs, and bacteria have the capability of sharing these mechanisms across different species types.⁴⁷ Today, the growing resistance of bacteria and viruses, including some organisms that are now wholly resistant to every available medicine, has become a global public health problem.⁴⁸

Strong, targeted basic research efforts and support for innovative therapeutic approaches towards fighting infectious diseases are the best way to move towards broad-spectrum protections. These are the strategies that are being pursued today.⁴⁹ However, as these efforts mature over time and pathways to safe and effective broad-spectrum countermeasures become available, it is important that policies are in place to take advantage of them. If the national and homeland security need for broad-spectrum protections is not made clear, government and academic researchers, as well as private sector companies, which have largely abandoned antimicrobial drugs and vaccines for commercial reasons,⁵⁰ will also fail to take advantage of advances in basic science that could lead to usable and distributable products.

⁴⁴ For example, see Celia Henry, "New Approach to Antibiotics," *Chemical and Engineering News*, April 12, 2004, 4.

⁴⁵ Charles Hackett, "Innate Immune Activation as a Broad-Spectrum Biodefense Strategy: Prospects and Research Challenges," *Journal of Allergy and Clinical Immunology*, 112, no. 4 (October 2003):686-694.

⁴⁶ Nicholas Valiante and others, "Innate Immunity and Biodefense Vaccines," *Cellular Microbiology*, 5, no. 11 (November 2003):755-780.

⁴⁷ Institute of Medicine, *Antimicrobial Resistance: Issues and Options*, (Washington, D.C.: National Academy Press, 1998).

⁴⁸ Institute of Medicine, *Microbial Threats to Health: Emergence, Detection, and Response*, (Washington, D.C.: National Academy Press, 2003).

⁶⁰ Defense Science Board, *2001 Summer Study on Defense Science and Technology*, May 2002, 112-115; <http://www.acq.osd.mil/dsb/sandt.pdf>.

⁴⁹ (a) Caitlin Harrington, "Pentagon in Race for Silver Bullet to Defeat All Terror Bugs," *Congressional Quarterly-Homeland Security*, October 27, 2003; (b) *Pathogen Countermeasures Program*, Defense Sciences Office, Defense Advanced Research Projects Agency, <http://www.darpa.mil/dsp/thrust/biosci/upathcm.htm>.

⁵⁰ Infectious Disease Society of America, *Bad Bugs, No Drugs: Defining the Antimicrobial Availability Problem*, Infectious Disease Society of America Backgrounder, November 2003, http://www.idsociety.org/Template.cfm?Section=Policy_and_Advocacy.

Broad-Spectrum Recommendation

Project Bioshield and any successor policies designed to spur the development and procurement of biodefense countermeasures should, in part, be explicitly directed towards filling the goals of broad-spectrum protections. The Departments of Homeland Security and Health and Human Services need to issue well-defined requirements for such countermeasures and direct the activities of their government, academic, and industrial research and development partners towards making these products a reality.

Rapid Countermeasures Development and Production: Moving Fast from Bug-to-Drug

Most drugs and vaccines today are developed to target a specific disease. As noted above, the process of making medicines available to physicians and patients, known as drug development, is typically very long and can be extremely costly. A targeted effort to reduce this timeframe and cost for biodefense countermeasures, that is to go from “bug-to-drug,” could allow the rapid discovery, development, and production of medicines needed to save lives after the pathogen has been identified.⁵¹ With such an approach, familiar agents that have been bioengineered to avoid existing countermeasures could be quickly analyzed to determine alterations. Existing countermeasures could then be tested and modified to defeat these changes. Alternatively, highly adaptable countermeasure technologies might be employed that can target pathogens specifically once identified. The production of proteins called monoclonal antibodies and certain new vaccines technologies are particularly promising approaches for this strategy.⁵² If faced with a completely new or unexpected agent, large “libraries” of existing drugs and other “drug-like” chemicals could be rapidly screened for their ability to kill or disrupt the pathogen by using high-speed, robotic systems, similar to those already used in the private sector.⁵³

New technologies and systems will also be required for the rapid determination of the safety and effectiveness of new countermeasure, even if they are to be deployed under emergency conditions.⁵⁴ Approaches here will likely include using gene or protein chips for rapid detection of common toxic side effects of potential medicines, computer-based modeling and simulation of complex biological systems, such as the human immune system, and development of cell and tissue cultures, including three-dimensional engineered organ systems,⁵⁵ for testing.⁵⁶ Rapid, “high-

⁵¹ Bradley A. Smith, Thomas V. Inglesby, and Tara O'Toole, “Biodefense R&D: Anticipating Future Threats, Establishing a Strategic Environment,” *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, 1, no. 3 (2003): 193-202.

⁵² Paul Dunman and Mirjana Nesin, “Passive Immunization as Prophylaxis: When and Where Will This Work?” *Current Opinion in Pharmacology*, 3, no. 5 (October 2002):486-496.

⁵³ (a) Jac Wijkman and R. Paul Beckett, “Combinatorial Chemistry in Anti-Infectives Research,” *Drug Discovery Today*, 7, no. 2 (January 2002):126-132; (b) Konrad Bleicher and others, “Hit and Lead Generation: Beyond High-Throughput Screening,” *Nature Reviews Drug Discovery*, 2, no. 5 (May 2003):369 – 378.

⁵⁴ Brian Paddle, “Therapy and Prophylaxis of Inhaled Biological Toxins,” *Journal of Applied Toxicology*, 23, no 3 (2003):139-170.

⁵⁵ *Rapid Vaccine Assessment*, Defense Sciences Office, Defense Advanced Research Projects Agency, <http://www.darpa.mil/dso/thrust/biosci/etc.htm>.

⁵⁶ Andrej Bugrim, Tatiana Nikolskaya, Yuri Nikolsky, “Early Prediction of Drug Metabolism and Toxicity: Systems Biology Approach and Modeling,” *Drug Discovery Today*, 9, no. 3 (February 2004): 127-135.

throughput” systems for determining important pharmacological properties and ability to kill pathogens will also be required.⁵⁷ Databases of genomic and proteomic information for humans and microbes would function as essential resources for these techniques.⁵⁸ Animal studies will also be important, since they offer working models of human physiology, can be conducted quickly, and allow certain experiments that would be unethical in humans. Ultimately, a strategic approach should seek to minimize the use of animal studies, and move towards faster and cheaper computer and tissue-based systems.⁵⁹ All of these approaches would speed development of countermeasures by shortening the long and time-consuming studies in people and laboratory animals currently employed. During an epidemic, methods and networks for conducting and sharing the results of experiments with potential therapies in patients should also be developed.⁶⁰ Finally, chemical and biologic manufacturing technologies and capacity should be examined and improved to meet rapid production requirements.⁶¹ There are significant opportunities for advances in these areas. The Defense Science Board has suggested that radical reductions in this process, from over a decade to as little as 24 hours, might be possible within 20 years (Figure 1).⁶²

The pathway from “bug-to-drug” is a complex, interdisciplinary system of systems. In its current state, significant uncertainty is encountered at various steps and the entire process requires years to negotiate. However, it is a conceptual and operational approach that has consistently led to safe and effective medicines in the past, and is now the standard pathway to developing new medicines. Radical shortening of the drug development process for new countermeasures will not be an easy task, and numerous technical and non-technical hurdles exist. But if broad-spectrum protections are not forthcoming or successful, developing and introducing a new drug or vaccine will be the only option for protection against new or bioengineered pathogens. Time, in addition to the pathogen, will become a deadly enemy.

In a recent report, the Food and Drug Administration (FDA), which monitors and regulates the entire drug development process, highlighted the lack of attention to safety, efficacy, and manufacturing technology challenges, and described this as a barrier to rapid and improved drug development.⁶³ According to FDA, “the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. Not enough new tools to get fundamentally better answers about the safety and effectiveness of new products can

⁵⁷ (a) Jürgen Bajorath, “Integration of Virtual and High-Throughput Screening,” *Nature Reviews Drug Discovery*, 3, no. 11 (November 2003):882-894; (b) Andrew Sharff and Haran Jhoti, “High-Throughput Crystallography to Enhance Drug Discovery,” *Current Opinion in Chemical Biology*, 7, no. 3 (June 2003):340-345; (c) Steve Buchanan and others, “The Promise of Structural Genomics in the Discovery of New Antimicrobial Agents,” *Current Pharmaceutical Design*, 8, no. 13 (2002):1173-1188.

⁵⁸ Steven A. Haney and others, “Genomics in Anti-Infective Drug Discovery – Getting to Endgame,” *Current Pharmaceutical Design*, 8, no. 13 (2002):1099-1118.

⁵⁹ Michael Hopmeier and Mary Esther, “Too Many Germs, Too Few Monkeys,” *Update: Food and Drug Law, Education, and Regulation*, no. 2, (March/April 2004): 21-27.

⁶⁰ Matthew P. Muller and others, “Clinical Trials and Novel Pathogens: Lessons Learned from SARS,” *Emerging Infectious Diseases*, 10, no. 3 (March 2004): 389-394.

⁶¹ (a) David Molowa and Rosemary Mazanet, “The State of Biopharmaceutical Manufacturing” in *Biotechnology Annual Review*, vol. 9, M.R. El-Gewely, Ed. (Amsterdam: Elsevier, 2003):285-302; (b) Neil Anderson, *Practical Process Research and Development*, (San Diego, Academic Press, 2000).

⁶³ U.S. Food and Drug Administration, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, March 2004, <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>.

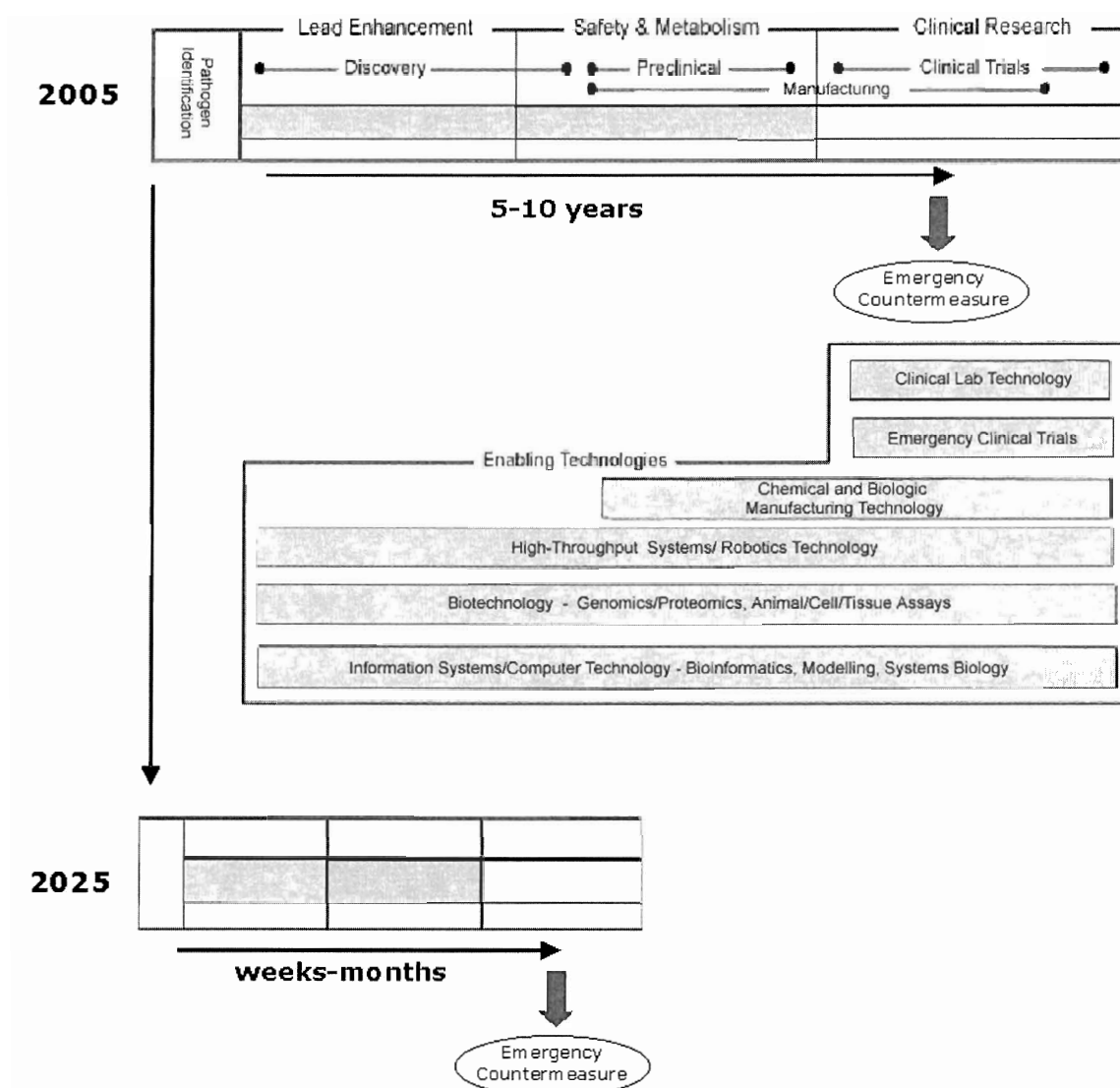


Figure 1. Shortening the pathway from “bug-to-drug” could be possible with a focused investment in enabling technologies to improve the various stages of the drug and vaccine development process.

be demonstrated, in faster timeframes, with more certainty, and at lower costs.” As a result, there is a “technological disconnect between discovery and the product development process....In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century’s candidates.”

Solving problems in rapid and accurate safety and efficacy prediction, as well as in manufacturing, are crucial steps for building a rapid “bug-to-drug” capability. These same advances will also significantly lower costs and lead to faster development for many types of new medicines.⁶⁴ Thus, there are substantial gains for health care to be reaped from such an investment. However,

⁶⁴ Joseph DiMasi, “Tufts CSDD Quantifies Savings from Boosting New Drug R&D Efficiency.” *Tufts Center for the Study of Drug Development Impact Report*, 4, no.5 (September/October 2002), <http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/ImpRptOct2002.pdf>.

because such advances could mean higher profits for companies, the private sector has an incentive to tackle these problems. But institutional factors are blocking progress. FDA points out that few organizations have the capability or incentives to look at the entire picture of this complex, system-of-systems problem.⁶⁵ Moreover, limitations on capital, a lack of cooperation among private firms, and a limited ability to capture the value of investments in fundamental improvements in discovery and development technologies have hampered a focused investment in dramatic reduction in the drug development timeframe.⁶⁶ To be sure, incremental improvements in drug and vaccine discovery, development, and production technologies are constantly being integrated into commercial processes. However, pharmaceutical, and an increasing proportion of biotechnology companies, focus the vast majority of their efforts on bringing innovative medical products to market, where significant returns on investment can be obtained even within the existing, slow drug development process.⁶⁷ The existing technology of the process is “locked-in” to the extent that, for those private firms developing medicines today, it is not profitable to spend time creating fundamental advances to speed discovery, development, and production. Meanwhile, the federally funded biomedical research enterprise tends to focus on basic research questions unrelated to development.⁶⁸ As a result of these factors, these advances are not subject to a coordinated, focused effort, and will take time to evolve.

An additional problem hampering the development of a rapid “bug-to-drug” capacity is the current regulatory environment. Requirements which must be met to successfully market a medical product are based on existing technologies and are slow to change, discouraging the investment in and adoption of novel approaches.⁶⁹ This is especially problematic because the rapid deployment of countermeasures to defeat previously unknown or engineered pathogens or toxins implies little or no advanced human clinical testing. Under such conditions, liability for damages can be a serious concern for any entity producing, distributing or administering a medical product, discouraging innovation and participation in the rapid development and deployment of countermeasures.⁷⁰ For biodefense purposes, Congress has already authorized the abridgement of the long testing and approval process required to ensure safety and efficacy under the emergency conditions of a severe outbreak of a harmful pathogen.⁷¹ However, even under emergency circumstances and if all liability concerns are resolved, it will still take years for even an experimental treatment or vaccine to become available.

Finally, as noted above, private sector firms are abandoning all types of innovation and research and development in the area of infectious diseases, in favor of investments in more profitable medical markets.⁷² Technologies and strategies specific to countering pathogens are increasingly only of interest to government for security or public health purposes. As a result of

⁶⁵ U.S. Food and Drug Administration, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, March 2004, 13.

⁶⁶ (a) Congressional Research Service, *Pharmaceutical Research and Development A Description and Analysis of the Process*, by Richard E. Rowberg, RL30913, April 2, 2001; (b) Ronald T. Borchadt, “Integrating Drug Discovery and Development,” *The Scientist*, 15, no. 5 (March 2001):43.

⁶⁷ (a) Andrew Pollack, “Is Biotechnology Losing It’s Nerve?” *New York Times*, February 29, 2004, Section 3, 1; (b) “Fixing the Drugs Pipeline” *The Economist*, March 13, 2004.

⁶⁸ Clifton Leaf, “Why We’re Losing The War On Cancer (And How To Win It),” *Fortune*, March 22, 2004, 76.

⁶⁹ Scott Gottlieb, “Developing the Biomedical Century,” *The American Enterprise*, March 2004, 32.

⁷⁰ Alan Pemberton, for the Pharmaceutical Research and Manufacturers Association, Testimony before the House Select Committee on Homeland Security, May 15, 2003.

⁷¹ Title XVI, National Defense Authorization Act for Fiscal Year 2004, PL 108-136.

⁷² (a) Roxanne Nelson, “Antibiotic Development Pipeline Runs Dry,” *The Lancet*, 362, no. 9397 (2003): 1726-1727; (b) Tom Clarke, “Drug Companies Snub Antibiotics,” *Nature*, 425, no. 6955 (2003): 225.

all of these factors, a collaborative, concerted effort in improving the medical product development process is now urgently needed for national security and, increasingly, public health reasons. As the FDA states, “if we do not work together to find fundamentally faster, more predictable, and less costly ways to turn good biomedical ideas into safe and effective treatments, the hoped for benefits of the biomedical century may not come to pass, or may not be affordable.”

Bug-to-Drug Recommendation

A coordinated, focused national strategy must be developed with the aim of achieving significant, dramatic, and continuous reductions in the timeframe from the identification of a previously unknown or engineered pathogen or toxin to the development and emergency approval for human use of reasonably safe and effective countermeasures. The Department of Homeland Security, in conjunction with the FDA, NIH, and the Department of Defense, should oversee an end-to-end assessment of the entire drug and vaccine development process. Bottlenecks and key technological gaps should be identified. Research and development strategies to resolve these technological barriers should be described and federal, academic, and private sector efforts currently underway in this area identified. Based on the needs and the extent of current efforts, a comprehensive research program, founded on policies allowing close public-private cooperation should be developed.

A clear strategy is also required to identify the specific capabilities and resources the United States will need make a rapid “bug-to-drug” response capacity a functional part of our biodefenses. As the existing and emerging technologies we will need are identified, a plan must be in place to make them available for rapid pathogen response. Mechanisms for the conduct of clinical trials during an infectious disease outbreak must be developed and put in place. The availability of appropriate manufacturing capacity for an adequate response must be assured.

No single federal agency has the mission or programmatic responsibility and expertise to consider all aspects of the new or bioengineered pathogen threat, the drug and vaccine development process, and manufacturing. A collaborative effort will clearly be required. The Department of Homeland Security should function as the “systems integrator” to ensure that its own science and technology resources, and those of other agencies, are combined with the expertise and capacities of the academic and private biomedical research sectors.

Conclusion

The emergence of biotechnology as a powerful tool for manipulating nature is well underway. For the most part, our health, environmental, and other consumer needs will drive the application of biotechnology to the benefit of humankind. However, as biological weapons become an increasingly desirable tool for terror and warfare, biotechnology will inevitably be applied towards these evil ends as well. National, homeland, and economic security demand a significant and prudent investment in biodefense to counter this evolving threat.

A government-sponsored investment in biodefense technology will reap huge benefits for society beyond just deterrence and protection against future biological weapons use. New broad-spectrum medical treatment strategies against infectious diseases are desperately needed as new diseases emerge from the environment and existing pathogens become resistant to treatments. At the same time, tremendous potential exists for benefits to health by concerted, targeted public-private investments in reducing the timeframe for the development of new countermeasures. Many of the fundamental and applied discoveries and technologies that result will find broad application across medical innovation. The pharmaceutical and biotechnology industries and biomedical research community are quick to integrate new technologies and important discoveries and advances will be rapidly absorbed, leading to faster delivery and reductions in costs of new medicines. The enormous potential pay-off and increasingly clear need to confront the emerging biological threat make such investments an obvious choice for America as we face the future.